Please add the following new claims:

28. (New) A multiparticulate bisopr lol formulation according to Claim 11, wherein the or each polymer is a methacrylic acid co-polymer.

29. (New) A multiparticulate bisoprolol formulation according to Claim 11, wherein the or each polymer is an ammonio methacrylate co-polymer.

30. (New) A multiparticulate bisoprolol formulation according to Claim 13, wherein a mixture of said polymers is used.

Please delete the following claims without prejudice:

Claims 26 and 27.

REMARKS

Claims 5-25 and 27 are objected to as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. The Examiner further states that Claims 5-7, 9-15, 17-22, 24 and 27 are improper multiple dependent claims. Also, Claims 8, 16, 23 and 25 depend upon the above-stated improper multiple dependent claims and are objected to as such. In response to these objections, applicants have amended Claims 5-7, 9-15, 17-22 and 24 to remove the multiple dependency language. Applicants note that Claim 3 was also a multiple dependent claim which has now been amended to depend only from Claim 1. Applicants now believe that Claims 5-25 are in proper format and can be examined on the merits.

Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by Busetti *et al.* (WO 98/32426). The Examiner indicates that Busetti *et al* teach a multiparticulate formulation comprising a core of a drug or its pharmaceutically acceptable salt surrounded by a polymeric coating. The Examiner further indicates that the polymeric coating is effective to achieve an initial lag between administration of the formulation and the release of the drug *in vivo* of at least 4-9 hours, but the lag time may be longer or shorter in certain cases. This is an incorrect statement by the Examiner as to the disclosed formulation in Busetti *et al*. Busetti *et al.* show no

in vivo data whatsoever. Each example in Busetti *et al.* demonstrates an *in vitro* dissolution time lag only. The *in vitro* dissolutions range from 302 ± 56 minutes (5 hours ± approximately one hour), greater than 300 minutes (5 hours), 8 hours, and greater than 6 hours. Claim 1 of the present invention defines a bisoprolol formulation having a polymeric coating that is effective to achieve an initial lag of bisoprolol release *in vivo* of at least 4 - 6 hours following administration. The 4-6 hour *in vivo* lag corresponds to an unexpectedly short *in vitro* dissolution lag where, for example, 27.3% of the active ingredient is released at 4 hours (See Table 1, Ex. 2 (A)) which corresponds to an *in vivo* lag of about 4 hours (See Fig. 3). Conversely, a longer *in vitro* lag matching that claimed by Busetti where less than 5% active ingredient was released at 4 hours (See Table 1, Ex. 5 (D)) produced a longer *in vivo* lag of about 10 hours (See Fig. 3). Based on the above, Claim 1 and dependent Claims 2-4 cannot be anticipated by Busetti *et al.* Consequently, applicants request withdrawal of the rejection of Claims 1-4 under 35 U.S.C.§102.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Busetti *et al* The Examiner further indicates that while Busetti *et al.* do not specifically teach a lag period of at least 3 hours, the reference does teach a lag period of 4-9 hours stating that the period may be shorter or longer. The Examiner further indicates that it would have been obvious to a person of ordinary skill in the art to adjust the lag time of the release of the drug *in vivo* either by increasing or decreasing the lag period to achieve the similar results. The Examiner is suggesting a 1:1 relationship between *in vitro* dissolutional and *in vivo* appearance of drug. What the Examiner has failed to note is that the longer *in vivo* lag period of 4-6 hours obtained in the present invention is surprisingly achieved via a shorter *in vitro* lag period of time. Please see page 5, line 13, where the applicants of the present application indicate that they found little correlation between *in vitro* release and *in vivo* plasma concentration required to achieve the desired therapeutic effects. Busetti clearly defines "lag" as that period of time during which there is no release of drug from the core. Again the *in vitro* dissolution time lags set forth in the Busetti examples range from 5 hours up to 8 hours. According to the Busetti definition, that means no drug is released until 5 hours after the formulation has been placed into a dissolution bath. In contrast, applicants would like to point out that Claim 5 of the present invention can have up to 50% release of total bisoprolol after 4 hours of measurement in a dissolution bath apparatus and

still achieve the desired 4-6 hour *in vivo* lag. More importantly, applicants emphasize again that the lag in Busetti *et al.* is an *in vitro* lag with absolutely no supporting data indicating whether an appropriate *in vivo* lag is obtainable. Applicants assert that the Examiner has failed to establish a *prima facie* obvious rejection of Claims 1-4. For these reasons, the applicants request withdrawal of the rejection of Claims 1-4 under 35 U.S.C. § 103 as being unpatentable over Busetti *et al.*

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

The Commissioner is hereby authorized to charge deposit account no. 05-0670 the amount of $54.00 for the additional claims. This amount is believed to correct; however, the Commissioner is authorized to charge any additional fees which may be required to the above account.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE

I hereby certify that this document is being transmitted via facsimile to the Commissioner of Patents and Trademarks, Washington, D.C. 20231, on this 1st day of June, 2001.

Tabitha E. Berris